Asthma and coagulation: A clinical and pathophysiological evaluation

Majoor, C.J.

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Chapter 9

Summary and general discussion
Summary

Background of the thesis
Clinical observations by asthma experts suggested that patients with severe asthma were at increased risk to develop venous thromboembolism (VTE). This is in line with findings in other inflammatory diseases like colitis ulcerosa and rheumatoid arthritis. It is well known that inflammation and hemostasis are closely linked and highly integrated systems. Inflammation almost inevitably leads to activation of hemostasis and vice versa. Therefore, the first part of this thesis focussed on the interaction between asthmatic inflammation and hemostasis. Clinical and physiological relevance for this interaction is investigated in a cohort of 648 patients with moderate to severe asthma, and in an observational study of 93 patients with asthma and 33 healthy subjects. In the second part attention is shifted to the main treatment of asthma exacerbations, oral prednisolone. In the first chapter of the second part of this thesis the clinical relevance is investigated in a large patient cohort. In the following two chapters the physiological interaction between hemostasis and oral prednisolone is investigated in a randomized double blind placebo controlled clinical study in patients with asthma and healthy subjects. Finally, in part three, the effect of specific asthma exacerbations on hemostasis is investigated in an observational study of a mild rhinovirus infection in patients with mild asthma and healthy subjects. The main results and conclusions, and implications are summarized below.

Summary of the studies
In the first part of this thesis we have reviewed the current literature on asthmatic airway inflammation and hemostasis in CHAPTER 2. Patients with asthma display signs of enhanced activation of coagulation in their airways upon allergen challenge, platelet activation, impaired function of the anticoagulant system (protein C and antithrombin III) and attenuated fibrinolysis. Protease activated receptors (PARs) have been identified as the link between coagulation and inflammation in experimental asthma. PAR2 activation, either by clotting proteases or proteases expressed by common allergens, contributes to disease severity.

In CHAPTER 3 we investigated the incidence of deep-vein thrombosis (DVT) and pulmonary embolism in outpatients with mild-moderate and severe asthma, and compared the incidence rates to an age-, and gender-matched reference population. 648 patients with asthma (283 with severe and 365 patients with mild-moderate asthma) visiting 3 Dutch outpatient asthma clinics, were studied. All patients completed a questionnaire about a diagnosis of deep-vein thrombosis and pulmonary embolism in the past, their risk factors, history of asthma and medication use. All venous thrombotic events were objectively verified. In this study we
described that patients with asthma, especially severe asthma, are at increased risk to develop pulmonary embolism but not DVT. In patients with severe asthma this risk is even 8.9 times higher than in the general population. This increased risk is associated with asthma severity (hazard ratio 3.3) and use of oral glucocorticosteroid use (hazard ratio 2.8). These results suggest that the incidence of pulmonary embolism is increased in patients with severe asthma, particularly in patients using oral corticosteroids.

In **CHAPTER 4** we further investigated the effect of asthma severity on hemostatic activation in a cohort of 93 patients with stable asthma of different severities and 33 healthy subjects. We compared markers of hemostasis and fibrinolysis and the thrombin generation test between healthy subjects and patients with mild asthma, severe asthma and severe prednisolone asthma. We showed that patients with stable asthma have an increased procoagulant activity as compared to healthy subjects. This increased procoagulant activity is shown by the increased levels in several key markers of the hemostatic system, like increased levels of plasminogen activator inhibitor type 1 (PAI-1), plasmin-α2-antiplasmin complexes (PAPc), and von Willebrand factor (vWF) levels in peripheral blood and an enhancement in the thrombin generation test with increased levels of peak thrombin, velocity index and endogenous thrombin potential (ETP). Furthermore, increased procoagulant activity is associated with asthma severity. In addition, there is a correlation between vWF and ETP with neutrophils, but not with eosinophils. These results imply that in patients with asthma, in particular patients with severe disease, coagulation is activated and therefore asthma may predispose for development of venous thromboembolism.

In the second part of this thesis we focussed on the influence of corticosteroids on hemostasis and more specifically in patients with asthma and healthy subjects. For several decades it has been thought that corticosteroids are procoagulant. However, clinical relevance has not been investigated. Therefore in **CHAPTER 5** the risk of symptomatic pulmonary embolism in patients using corticosteroids was evaluated using the PHARMO Record Linkage System, a Dutch population based pharmacy registry. In total 4,495 patients with a first hospital admission for PE between 1998 and 2008 were matched to 16,802 sex- and age-matched control subjects without a history of PE. Oral glucocorticosteroids were found to have a fourfold increased risk of pulmonary embolism in a time- and dose-dependent relation. The highest risks were observed in the first 30 days of glucocorticosteroid use (sixfold increased risk) and for the highest daily dose (10-fold increased risk). But also in low-dose glucocorticosteroid users, the highest risk of pulmonary embolism (2.8-fold increased risk) was observed in the first 30 days after initiation of treatment as compared to long-term users.
To further investigate the effect of corticosteroids on hemostasis we performed a randomized double-blind placebo-controlled study to evaluate the effect of short burst prednisolone course on hemostasis in patients with asthma and healthy subjects. In CHAPTER 6 we described the effects of prednisolone in 60 patients with stable asthma of different severities. Patients received 0.5mg/kg/day of prednisolone for 10 consecutive days. Patients in the prednisolone group had increased levels of vWF (20%), PAI-1 (37%, change of 8ng/ml) and decreased levels of PAPc (-11.5%, change of 51.4 µg/L). Although no change occurred in thrombin-antithrombin complexes (TATc) and D-dimer, thrombin generation increased, as peak thrombin and velocity index were increased by respectively 11% and 25%. Peripheral blood eosinophils, CRP and FeNO decreased, while neutrophils increased. We concluded that a 10-day course of oral prednisolone (0.5mg/kg/day) in patients with stable asthma caused a shift in the hemostatic balance to a procoagulant state by increasing in vitro coagulation and reducing fibrinolysis. Activation of coagulation occurred despite an anti-inflammatory effect of oral prednisolone, as shown by a decrease in peripheral blood eosinophils, CRP and exhaled nitric oxide. This suggests that the prothrombotic state in asthma patients and the increased risk of thromboembolic events not only depends on disease activity, but also on the adverse effects of oral corticosteroids.

In CHAPTER 7 we described the effects of prednisolone in a group of 31 healthy subjects receiving a 10-day oral prednisolone course of 0.5mg/kg/day. Healthy subjects receiving a similar course of prednisolone as patients with asthma, also had an increase of 18% in vWF and 80% (4.6 ng/mL) in PAI-1, while no change was observed for PAPc. No change occurred for TATc nor for D-dimer, but thrombin generation increased in healthy subjects. Peak thrombin increased by 16% and velocity index by 41%. We concluded from this study that oral corticosteroids increase procoagulant activity in healthy subjects, suggesting that oral corticosteroid treatment may contribute to the reported thromboembolic risk in patients with inflammatory diseases.

In the last part of this thesis we investigated the effect of an infectious trigger on hemostasis in healthy subjects and patients with mild asthma. In CHAPTER 8 we investigated the effect of an experimental rhinovirus infection (Rhinovirus type 16 (RV16)) on hemostasis in an observational study. 14 healthy subjects and 14 patients with very mild atopic asthma (no maintenance dose of inhalational corticosteroids) were included in the study. Rhinovirus infection enhanced coagulation in patients with very mild asthma, but not in healthy subjects. Increased procoagulant activity in the pulmonary environment as evidenced by increased microparticle-associated TF activity in bronchoalveolar lavage (BAL) fluid was observed in patients with asthma. Moreover, the change in fibrin generation test and TATc correlated with markers of
eosinophil and neutrophil activation (respectively eosinophil cationic protein and myeloperoxidase) in BAL fluid. In addition to local procoagulant activity, RV16-load showed linear correlations with markers of fibrinolysis and hemostatic activity in plasma. Therefore rhinovirus infection increases the local procoagulant activity in the airways through both eosinophilic and neutrophilic airway inflammation as well as a rhinoviral load associated correlation with markers of fibrinolysis (PAPc and PAI-1) and procoagulant activity (ETP) in plasma.
General discussion

Comparison with current literature

Asthma and coagulation

In the first and third part of this thesis we focussed our research on the interaction between coagulation and asthma. We investigated the clinical relevance, the possible relation with asthma severity and the effect of a rhinovirus infection on coagulation in asthma patients. Previous research on asthma and coagulation focussed on coagulation in the airways of patients with primarily atopic asthma. Increased amounts of TF, TATc and fibrin are found in induced sputum and BAL fluid of patients with asthma as compared to healthy subjects. Activation of coagulation can be initiated by allergens, viruses (chapter 8) and possibly also by fungi and air pollution. No studies were performed to evaluate coagulation in plasma let alone evaluate the clinical consequences of its activation in asthma. In other inflammatory diseases like rheumatic arthritis, colitis ulcerosa, Crohn’s disease, glomerulonephritis, chronic rhinosinusitis and COPD, coagulation is activated and an increased risk to develop venous thromboembolism is observed.

In chapter 4 we described a correlation between activation of hemostasis in plasma and asthma severity. Previous research showed such a correlation in induced sputum of patients with asthma with different severities. Others showed a correlation between TATc and an increase in airway hyperresponsiveness and sputum eosinophilic cationic protein in patients with asthma. However we did not find an association with eosinophils but rather with neutrophils, which can be explained by the fact that we studied patients with stable asthma in which eosinophilia is depleted and the neutrophilia is induced by oral prednisolone. The highest levels of procoagulant markers were observed in the group of patients with oral prednisolone-dependent asthma. And although neutrophils are capable of activating coagulation, we believe that the association observed in this study is related to the study design. Nevertheless the association between asthma severity and coagulation is not only found in the airways, but also in blood. Whether activation of coagulation is eosinophilic or neutrophilic may depend upon the inflammatory trigger.

Activation of coagulation in asthma is among others initiated by allergens. In chapter 8 we observed that a mild rhinovirus infection activates coagulation in the airways and blood of patients with mild asthma, but not in healthy control subjects. Activation of coagulation in blood in patients with asthma was associated with the rhinoviral load in BAL fluid. Not much is known about activation of hemostasis by non-hemorrhagic non-herpes viral infections in humans. Influenza like illness (ILI) has been shown to activate coagulation in elderly people. In a cohort of 115
elderly subjects 15 developed ILI in the subsequent months. Most patients were infected with influenza (n=6) and parainfluenza (n=3), but in none of the patients with symptoms of ILI rhinovirus was detected. Recent evidence showed that PAI-1 levels were increased in induced sputum and nasal fluid of patients with asthma during common colds. Rhinovirus was the most prevalent virus in this group of 52 patients with asthma and 14 healthy subjects. Unfortunately only PAI-1 was studied and no other hemostatic markers, as PAI-1 may also be an acute phase protein and increases upon mild stimulation. This shows that not only allergens, but also viral infections like influenza, rhinovirus and may be other viruses, like parainfluenza and RS-virus, are likely to trigger coagulation in patients with asthma. Maybe also other factors can trigger coagulation in asthma, like fungi, air pollution or exercise.

The enhanced coagulation in plasma of patients with moderate-severe asthma and procoagulant triggers suggest that patients with asthma may have thromboembolic complications. In chapter 3 we described that patients with asthma are at increased risk to develop pulmonary embolism. This risk was associated with asthma severity and oral prednisolone use. Even more interesting was the observation that pulmonary embolism occurred twice as often as deep venous thrombosis. This association was also found in patients with COPD and sarcoidosis. In a large cohort analysis from Taiwan, Chung et al. confirmed the increased risk to develop pulmonary embolism. Patients with asthma had a more than threefold increased risk to develop pulmonary embolism and this risk increased rapidly with the increasing number of asthma exacerbations. Apparently patients with asthma and frequent disease exacerbations are at increased risk to develop also other thromboembolic events, such as acute coronary events and stroke. A risk that was also associated with disease exacerbations and use of oral corticosteroids.

Corticosteroids and coagulation

Previous studies in inflammatory diseases and healthy subjects suggested that prednisolone is prothrombotic. Secondly, in patients with Cushing’s disease an increased risk to develop VTE has been described and a procoagulant state in the plasma of patients with Cushing’s disease has been found. Nevertheless, no studies have been performed on the risk of corticosteroid treatment and pulmonary embolism. In chapter 5 we described that patients using oral corticosteroids are at the highest increased risk (sixfold increased) to develop VTE shortly after the start of therapy. However, also chronic low dose treatment with oral corticosteroids increased the risk to develop VTE (hazard rate 2.2). A second larger Danish study showed more or less identical results on oral corticosteroids (Incidence rate ratio of 3.1). Patients with pulmonary diseases using inhalational corticosteroids (ICS) did not have an increased risk to develop VTE except at the initiation of ICS.
treatment (Incidence rate ratio of 2.2)\(^{39}\). A British study investigating the incidence of VTE in the general population and potential risk factors, showed a threefold increased risk for oral corticosteroids\(^{40}\). The major problem with these associations is that although statistical adjustments are made for potential confounding factors, such as immobility, and infection, residual, unmeasured, confounding cannot be ruled out.

Several studies investigated the effect of oral corticosteroids on coagulation and fibrinolysis. The design, intervention and study populations differed very much. We investigated the effect of oral prednisolone in patients with stable asthma and healthy subjects (Chapter 6 and 7). This way we were able to investigate the effect of prednisolone on coagulation and were not influenced by the inflammatory effect of asthma. We showed that both healthy subjects and patients with asthma have an enhanced coagulation and observed a reduction in fibrinolysis in patients with asthma. Two studies investigated coagulation in healthy subjects\(^{41,42}\), and three investigated PAI-1 and D-dimer\(^{41,43,44}\). These studies showed no major changes in TATc\(^{42}\), and no change in PAI-1 after 5 days of oral dexamethasone\(^{41}\). However an increase of 10-20% in several coagulations factors (Factor VII, VIII and XI) were observed in healthy subjects\(^{41}\). Especially the last finding is in line with the 13-15% increase we observed in peak thrombin in both healthy subjects and patients with asthma. Other studies in patients with inflammatory diseases showed a decrease in TATc\(^{45,46}\), and vWF\(^{47,48}\) and an increase in PAI-1\(^{45-47}\). However, several of these studies investigated the effect of prednisolone in patients with acute exacerbations of inflammatory diseases. Acute exacerbations are associated with intense inflammatory processes, which concurrently activates coagulation. Therefore the true effect procoagulant effect of oral prednisolone cannot be evaluated, as results are influenced by the acute inflammation\(^{45-47}\).

The effect of oral corticosteroids on activation of coagulation as described in studies is discordant in patients with inflammation. As described above some studies observed a decrease of the prothrombotic state in patients with inflammatory diseases\(^{45,46}\). In contrast, activation of coagulation and an increase of fibrinolysis upon treatment with oral prednisolone were shown in a study evaluating the effect of prednisolone in a sepsis model with lipopolysaccharide (LPS). Healthy subjects receiving high doses of oral prednisolone had a larger increase of procoagulant activity in the first 4 hours after challenge with LPS as compared to healthy subjects receiving no prednisolone\(^{49}\). Another interesting observation was shown in patients with a solid organ transplant. Patients with kidney transplant have a procoagulant activity, which disappears after the oral prednisolone is stopped and replaced by other immunosuppressive drugs\(^{50}\). These are all interesting observations that need further exploration.
Interpretations of the results of this thesis

Previous groups have shown that coagulation is activated in the airways of patients with asthma. In this thesis we have shown that coagulation is also activated in the blood of patients with asthma. How can the activation of coagulation in asthma and the prothrombotic nature of corticosteroids fulfil the criteria of Virchow’s triad of hypercoagulability, endothelial activation and stasis of bloodflow and result in the observed increased incidence of pulmonary embolism?

Hypercoagulability in patients with asthma is initiated by disease exacerbation or disease progression. Several triggers can induce an asthma exacerbation like allergens\textsuperscript{6,51,52}, viruses\textsuperscript{53,54}, fungi\textsuperscript{49}, air pollution\textsuperscript{55,56}, and aspecific triggers like exercise, temperature changes, and humidity\textsuperscript{56}. Not all of these triggers may activate coagulation. In allergen challenged patients with asthma, TF and microparticle-associated TF have been shown to be enhanced in the airways\textsuperscript{3,5}.

In chapter 8 we showed that upon rhinovirus infection, microparticle-associated TF initiated coagulation in BAL fluid in patients with mild asthma. TF initiates the extrinsic coagulation pathway by forming a complex with factor VII. TF is expressed by several cells involved in asthmatic inflammation. Beside airway epithelial cells and endothelial cells, lymphoid cells, and leucocyte-derived microparticles, also eosinophils have been shown to express TF\textsuperscript{57-60}. TF is expressed upon cell death. Upon destruction of airway epithelial cells or inflammatory cells in the airways, TF is expressed and the coagulation cascade may be initiated. However, some authors have suggested that plasma leakage may explain the increased amounts of coagulation factors in the airways\textsuperscript{61-63}. Some studies investigating coagulation in patients with asthma corrected for plasma leakage by using the α2-macroglobulin-albumin ratio and still showed that TF increased while coagulation factors VII, X and XIII decreased in induced sputum\textsuperscript{1}.

Beside local hypercoagulability in the airways, activation of coagulation in blood of patients with asthma has been shown in disease exacerbations, for example with allergen challenge\textsuperscript{5,6} and rhinovirus (Chapter 8). We showed in chapter 4 that also asthma severity correlates with a procoagulant state in blood. Activation of coagulation in more severe asthma may be related to recurrent exacerbations, systemic exposition of high dose inhalational corticosteroids\textsuperscript{64}, and/or oral corticosteroids use, as corticosteroids enhance coagulation by induction of TF expression and PAI gene transcription\textsuperscript{57,59,65}. However loss of asthma control showed no activation of coagulation in blood of patients with moderate-severe asthma\textsuperscript{66}.

Endothelial activation most likely occurs directly through the thin pulmonary blood/air barrier or indirectly through the release of mediators of affected cells. Activation of epithelial cells upon stimulation by allergens, viruses or other asthmatic stimuli may be possible triggers of endothelial cell activation. In chapter 8 we proposed that
rhinovirus probably activates endothelial cells indirectly through mediators released by infected epithelial cells or directly as endothelial cells express ICAM-1, the receptor that enables rhinovirus to infect human cells. Also allergen exposure activates the endothelial cells through the mediator release by affected epithelial cells.

Another option for endothelial activation could be oral corticosteroid use. In chapter 6 and 7 we proposed that corticosteroids activate endothelial cells and leucocytes in the absence of inflammatory stimuli leading to enhancement of vWF gene transcription. Interestingly, in a recent cross-sectional study it was shown that markers of activation of vascular endothelial cells correlate with areas of decreased ventilation in hyperpolarized Helium-3 Magnetic Resonance Imaging and multidetector CT scan in patients with severe asthma. This suggests that endothelial activation occurs in the affected/triggered areas of the asthmatic lung. Taken together these results suggest that endothelial cells are activated in patients with asthma.

The third criterium of Virchow’s triad, stasis of blood flow, is likely to occur in the asthma affected areas of the lung, and may be explained by local hypoxia. In asthma bronchoconstriction is not homogenous but more heterogenous, and thus some parts of the lung may experience local hypoxia. Hypoxia causes local hypoxic vasoconstriction to improve the ventilation-perfusion ratio in other parts of the lung. Even more, local hypoxia may also contribute to the activation of coagulation in the affected parts of the lung. Although conflicting evidence exists on hypoxia and activation of coagulation in healthy subjects, hypoxia has been shown to activate coagulation in patients with COPD. In a recent study patients with COPD were exposed to an inhaled oxygen fraction of about 15% (100% nitrogen via a 40% venturi mask at a flow rate of 10L/min) for two hours. After two hours of inhalation of hypoxic air, TATc and prothrombin fragment 1 + 2 increased, while D-dimer and vWF did not change. It is likely that also in other pulmonary diseases, like asthma, local hypoxia can occur and cause activation of coagulation. Hypoxic vasoconstriction and subsequent reduced blood flow could explain the third criterium of Virchow’s triad for thrombus formation. So, by activation of coagulation and endothelial activation by specific asthma triggers and oral prednisolone, and reduction in blood flow by local hypoxia through the asthmatic trigger, all three criteria of Virchow’s triad for thrombus formation are fulfilled.

Two other observations support this hypothesis. First, the affected parts of the lung enhance coagulation; the dilution of the coagulation factors by the blood flow from the unaffected parts of the lung may explain that we found small increases in coagulation factors in blood. Second, if local hypoxia in the lung activates coagulation locally in the lung, this may explain why in patients with pulmonary diseases, like asthma and COPD, the prevalence of PE is twice as common as DVT (Chapter 3), as compared to the general population, where the opposite
holds true\textsuperscript{76,77}. In pulmonary diseases, pulmonary embolism may occur by local thrombus formation rather than be embolization of thrombi from deep leg veins. Although this mechanism does not support the increased incidence for acute coronary syndrome and stroke, we believe that this could be an explanation for the increased incidence of pulmonary embolism in patients with asthma. One has to keep in mind that the observed risk for acute coronary syndrome and stroke is lower than the increased observed risk for pulmonary embolism. Possibly other factors contribute to the venous stasis in these events, as the hypercoagulability and endothelial activation by corticosteroid treatment still support the first two criteria of the Virchow’s triad.

**Clinical implications of this thesis**

As described before, inflammation and coagulation are very closely related and influence one another\textsuperscript{26,78-81}. The close interaction suggests that activation of coagulation by inflammation is also very important. For example, activation of coagulation by rhinovirus infection may prevent the rhinovirus from spreading through the body and contain the rhinovirus to the affected nose or respiratory system. Nevertheless uncontrolled activation of coagulation can induce thromboembolic complications.

In this thesis we have shown that the blood of patients with asthma is hypercoagulable by enhancement of coagulation and a reduction in fibrinolysis. The hypercoagulable state increases with asthma severity and is triggered by disease exacerbations, for example by rhinoviral infection, but also by allergic provocation\textsuperscript{3,5,7}. As a result we described an increased incidence of pulmonary embolism, while recently also an increased risk in acute coronary syndrome and stroke was observed\textsuperscript{31-33}. Secondly, endothelial activation is enhanced in patients with asthma, which may further contribute to the increased incidence in pulmonary embolism and other thromboembolic events. Patients with asthma, and especially severe asthma, should be closely observed for acute coronary events and pulmonary embolism, and in patients with ongoing exacerbations of asthma pulmonary embolism should be excluded.

A second major implication is the observation that oral prednisolone enhances coagulation and reduces fibrinolysis in patients with stable asthma and healthy subjects. Not only it provides better insight into the mechanisms why patients with severe asthma and frequent exacerbations are at increased risk for pulmonary embolism\textsuperscript{82}, but it also suggests that any patient receiving frequent bursts or chronic administration of oral corticosteroids are at increased risk to develop thromboembolic events\textsuperscript{39,83}. Most likely this reflects the increased incidence of pulmonary embolism observed with the use of corticosteroids. This implies that physicians should be alert for the development of pulmonary embolism when they initiate treatment with oral corticosteroids. Even more as the RIETE study group
(Computerized Registry of Patients with Venous Thromboembolism (RIETE)) recently showed that patients immobilized at home with acute medical illness are at increased risk to develop a fatal pulmonary embolism as compared to hospitalized patients. Therefore, it is critical to verify whether a patient really needs oral corticosteroids. In addition, patients with inflammatory diseases who need potent anti-inflammatory treatments, might be better off with anti-inflammatory biologicals, such as anti-TNFα-blockers in case of colitis and rheumatoid arthritis, or anti-IL-5 or anti-IL-4/IL-13 with asthma. Additionally, one might consider thromboprophylactic treatment in asthma patients during exacerbations or in those receiving chronic oral corticosteroid treatment. Of course, this needs further research.

Future research

Asthma and coagulation

In this thesis we showed that patients with asthma are at increased risk of pulmonary embolism due to a hypercoagulable state induced by asthma severity, asthma triggers and oral corticosteroid use. Future research should focus to further investigate procoagulant effects of the new anti-inflammatory biologicals for severe asthma, like anti-IL-5 and anti-IL-4/IL-13. If these medications reduce activation of coagulation in patients with severe asthma, these drugs may be used instead of oral prednisolone. This not only solves hypercoagulability, but also improves compliance and other corticosteroid related side-effects, like obesity, diabetes mellitus, and osteoporosis. However, this option may not work for patients with an acute exacerbation. These patients may still require oral prednisolone. To prevent these patients from developing thromboembolic complications, concurrent use of short-term thromboprophylaxis should be investigated, as especially disease exacerbations may further enhance coagulation. As patients with other inflammatory diseases also have an increased risk to develop a pulmonary embolism, this study should not be limited to patients with asthma exacerbations, but extended to patients with other inflammatory diseases, like COPD, inflammatory bowel disease, and connective tissue diseases.

Beside treatment of hypercoagulability, further research in patients with asthma should focus on three other aspects. First, basic science should further explore the precise interaction between coagulation and asthmatic inflammation. Previous research showed that PAI-1 gene (SERPINE 1) 4G/5G polymorphism is associated with airway hypersensitivity, more rapid decline in FEV1 and ICS response. Therefore further research is needed on the precise mechanism how the coagulation system enhances asthmatic inflammation and airway remodelling. Especially since asthma is characterized by different phenotypes which will lead to personalized treatment of asthma.
Second, more research should be performed on the mechanism of thrombus formation. Are pulmonary emboli formed in situ or are they being embolized from a venous thrombosis? Can the hypothesized local hypoxia explain the local formation of pulmonary embolism? And finally, diagnosis of pulmonary embolism in patients with pulmonary diseases is difficult. Since the introduction of the electronic nose in pulmonary medicine knowledge on the use of the E-nose has increased rapidly. Previous research has shown that pulmonary embolism can be detected with the Cyranose 320. Can the E-nose be used to distinguish between asthma or other pulmonary exacerbation, and a pulmonary embolism?

Corticosteroids and coagulation

Since the primary therapy for patients with asthma is inhaled and/or oral corticosteroid treatment, we also further investigated the interaction between corticosteroids and coagulation. The increased risk to develop pulmonary embolism and the procoagulant state induced by corticosteroids were shown. The precise mechanism through which prednisolone activates coagulation is unknown. Interaction between corticosteroids and the inflammatory disease presumably plays a role in the increased incidence of pulmonary embolism. Further research should focus on the precise mechanism on how corticosteroids enhance coagulation. Is it just by induction of gene transcription of PAI-1 and vWF or do corticosteroids have more effects on coagulation?

Conclusion

This thesis focussed on the interaction of coagulation, inflammation and corticosteroid treatment on asthma. In this thesis we showed that asthma, oral prednisolone and rhinovirus each enhance coagulation, which may result in venous thromboembolic events, pulmonary embolism in particular during exacerbations. And although we have become more aware of pulmonary embolism in patients with asthma, we cannot prevent the occurrence of venous thromboembolic complications yet. A striking example of this latter issue is the recent presentation in our clinic of a female patient with severe prednisolone-dependent asthma and a RS-virus pneumonitis, who developed bilateral pulmonary emboli during the course of her disease. In order to prevent the occurrence of these thromboembolic complications in patients with asthma, it is important that further research is performed to address the interaction between coagulation and inflammation in asthma and to further investigate the influence of corticosteroids on the interaction between the inflammatory and hemostatic systems in asthma and other inflammatory diseases.


38. van der Pas R, de Bruin C, Leebeek FW, et al. The hypercoagulable state in Cushing’s disease is associated with increased levels of procoagulant factors and impaired fibrinolysis, but is not reversible after short-term biochemical remission induced by medical therapy. *J Clin Endocrinol Metab.* 2012;97(4):1303-10.


